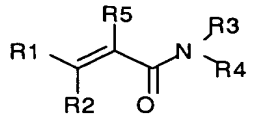
Patent claims

1. Method for the production of α,β-unsaturated amide compounds having the general formula (I):



(I)

wherein,

R_1 and R_2 are independently hydrogen; optionally linear or branched (C_1-C_{18}) alkyl or (C_1-C_{18}) alkenyl substituted with hydroxy, halogen, phenyl, substituted phenyl, or an ester group [-C(O)Oalkyl] or an amide group [$-C(O)NH_2$ or -C(O)NHalkyl]; optionally phenyl substituted with halogen; or

R_1 or R_2 comprises a group $Y-R_6$; in which

Y is oxygen (-O-); sulphur (-S-); $-NR_7-$; or dialkylsilyloxy [$-(alkyl)_2Si-O-$];

R_6 is hydrogen, optionally linear or branched (C_1-C_{18}) alkyl substituted with hydroxy, halogen, phenyl, substituted phenyl or with an ester group [-C(O)OAlkyl] or an amide group [$-C(O)NH_2$] or [-C(O)NHAlkyl]; optionally phenyl substituted with halogen;

R_7 is (C_1-C_{18}) alkyl or $-N(R_6)(R_7)$ is a 5- or 6-membered heterocyclic ring;

or

R_1 together with R_3 is directly bonded or a group having the formula $-(CH_2)_n-$; in which

n is a whole number from 1 to 12;

or

R_1 together with R_2 is cyclohexylidene;

or

R_1 together with R_5 and the incorporated (C=C)-double bond is cyclohexenyl;

or

R_1 together with R_5 and the incorporated (C=C)-double bond forms a group of a monounsaturated bicyclic ring;

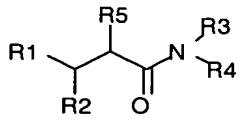
R_3 is hydrogen, optionally a linear or branched (C_1-C_{12}) alkyl substituted with phenyl, hydroxyl, or halogen, carrying one or more oxygen atoms, (C_5-C_8)-cycloalkyl or (C_5-C_8)-cycloalkenyl, carrying one or more oxygen atoms; preferably, phenyl substituted with halogen or hydroxyl; or R_3 together with R_1 is directly bond or forms a group of the formula $-(CH_2)_n-$;

R_4 has one of the meanings of R_3, preferably hydrogen, optionally linear or branched (C_1-C_{12}) alkyl substituted with phenyl, hydroxyl, or halogen, optionally phenyl substituted with halogen or hydroxyl; or $-NR_3R_4$ a 5- or 6-membered heterocyclic ring; and

R_5 has one of the meanings specified for R_1 or R_2 as independent substituents,

wherein said method comprises the steps of:

(A) reacting a compound of the general formula (II):



(II)

wherein R_1, R_2, R_3, R_4 and R_5 have the meanings specified above, to introduce protective groups so as to produce a compound of the general formula (III):

wherein R_8 is trialkylsilyl, or (when R_4 = hydrogen) together with R_9 forms the group $-C(O)-(CH_2)_m-C(O)-$ and

R_9 (when R_4 = hydrogen) is alkyloxycarbonyl or phenyloxycarbonyl, preferably Boc (= tert. butyloxycarbonyl); or trialkylsilyl, or together with R_8 the group $-C(O)-(CH_2)_m-C(O)-$, and

m is 0, 1, 2, or 3, preferably 0 or 1, preferably 0,

and in the case in which for the compound of the general formula (II) hydroxyl is present, it is reacted, with a monovalent protective group R_8 and/or R_9;

(B) reacting the compound obtained in step (A) in the presence of (i) a dehydrogenation catalyst and in the presence of (ii) an oxidising agent, such as optionally substituted benzoquinone, allyl methyl carbonate, allyl ethyl carbonate and/or allyl propyl carbonate,

to introduce an α,β-double bond in the α,β-position, and

(C) optionally removing, if present, the protective groups R_8, as well as the substituent R_9.

2. Method according to claim 1, wherein R_1 and R_2 are independently hydrogen, optionally linear or branched (C_1-C_8) alkyl or (C_1-C_8) alkenyl substituted with hydroxy, phenyl, phenyl substituted with halogen or hydroxy, or with a (C_{1-4}) alkyl ester group or an amide group or (C_{1-4}) alkyl amide group, preferably, phenyl substituted with

halogen; preferably linear or branched (C_1-C_8) alkyl or (C_1-C_8) alkenyl, benzyl or phenyl.

3. Method according to claim 1, wherein R_2 is hydrogen and R_1 is linear or branched (C_1-C_8) alkyl or (C_1-C_8) alkenyl, benzyl or phenyl or Y-R_6.

4. Method according to claim 1, wherein R_1 is hydrogen and R_2 is linear or branched (C_1-C_8) alkyl or (C_1-C_8) alkenyl; benzyl or phenyl or Y-R_6.

5. Method according to claim 1, wherein R_1 together with R_3 is directly bonded or forms a group of the formula -$(CH_2)_n$- and n is a whole number from 1 to 12; or R_1 together with R_2 is cyclohexylidene; or R_1 together with R_5 is cyclohexenyl.

6. Method according to claim 1, wherein Y in the group Y-R_6 is oxygen.

7. Method according to claim 1 wherein R_6 is hydrogen, optionally linear or branched (C_1-C_8) alkyl or phenyl substituted with hydroxy, halogen, phenyl, phenyl substituted with halogen, or an (C_{1-4})alkyl ester group or an amide group or a (C_{1-4})alkyl amide group; optionally phenyl substituted with halogen; preferably hydrogen, optionally linear or branched (C_1-C_8) alkyl substituted with phenyl, or with a (C_{1-4}) alkyl ester group or an amide group or a (C_{1-4}) alkyl amide group; or phenyl; preferably hydrogen, linear or branched (C_1-C_8) alkyl or phenyl.

8. Method according to claim 1, wherein the substituent $-N(R_6)(R_7)$ as heterocyclic ring is a pyrrolidine or piperidine.

9. Method according to claim 1, wherein the compound of the formula (II) represents a lactam of an omega amino fatty acid, preferably aminobutyric acid, omega aminovaleric acid, omega aminocapronic acid, or omega aminolauric acid.

10. Method according to claim 1, wherein the compound of the formula (I), R_1 together with R_5 and the incorporated (C=C)-double bond represent a monounsaturated bicyclic ring, preferably a norbornyl group optionally substituted with hydroxyl or amino, preferably a norbornyl group.

11. Method according to any of claims 1 to 10 wherein R_3 and R_4 are independently hydrogen, linear or branched (C_1-C_4) alkyl optionally substituted with phenyl, phenyl; or the group $-NR_3R_4$ is pyrrolidine or piperidine.

12. Method according to claim 1, wherein R_5 is hydrogen, tert. butyl or optionally phenyl substituted with halogen or hydroxyl, preferably hydrogen; and R_8 is trimethylsilyl or R_8 together with R_9 is the group $-C(O)-(CH_2)_m-C(O)-$; or R_9 is Boc, trimethylsilyl, or R_9 together with R_8 is the group $-C(O)-(CH_2)_m-C(O)-$, in which m is 0, 1, 2, or 3, preferably 0 or 1, preferably 0.

13. Method according to claim 1, wherein R_9 is alkyloxycarbonyl, isobutyloxycarbonyl, tert. butyloxycarbonyl, tertiary amyloxycarbonyl, cyclobutyloxycarbonyl, 1-methylcylobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl, 1-methyl-cyclohexyl, preferably tertiary butyloxycarbonyl.

14. Method according to one of the claims 1-13, wherein the dehydrogenation catalyst [in step (B)] is selected from amongst compounds (salts and complexes) of the transition metals of the periodic system, preferably from compounds of the metals of Group VIII elements, in particular from iron, ruthenium and osmium; cobalt, rhodium, and iridium; nickel, palladium and platinum; copper, silver and gold preferably from compounds based on rhodium, palladium and platinum.

15. Method according to claim 14, wherein the dehydrogenation catalyst is a palladium compound, preferably a Pd(0) compound, preferably a tris(dibenzylidene acetone) dipalladium chloroform complex or a Pd(II) compound, preferably $PdCl_2$, $Pd(dppe)_2$, $Pd(dppe)Cl_2$, $Pd(OAc)_2$, $Pd(dppe)(OAc)_2$, π-allyl Pd complex, preferably π-allyl Pd chloride dimer.

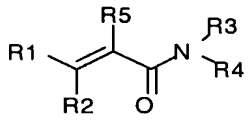
16. Method according to one of the claims 1-15, wherein an additional complexing agent is used for the thermal stabilisation of the palladium complex, preferably 2,2'-bipyridyl or 1,10-phenanthroline.

17. Method according to one of the claims 1-16; wherein the quinone is a substituted quinone, preferably a quinone substituted with C_{1-4} alkyl, halogen, cyano or nitro.

18. Compounds produced according to one of the claims 1-17.

Summary

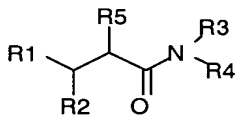
The invention relates to a method for production of α,β-unsaturated amide compounds having the general formula (I):



(I)

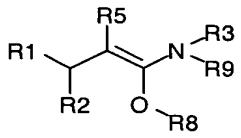
whereby

(A) the protective group is introduced into a molecule of general formula (II)



(II)

to give a compound of formula (III),



(III)

(B) the compound obtained is reacted in the presence of (i) a dehydrogenation catalyst and (ii) a suitable oxidation agent and

(C) the protective groups are removed.